BK VIRUS NEPHROPATHY IN A HEART TRANSPLANT RECIPIENT: THE FIRST DOCUMENTED CASE IN CROATIA

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As outcomes following heart transplantation have improved significantly over the last years, chronic kidney disease has become an increasingly prevalent complication in this population. Polyomavirus-associated nephropathy (PVAN) of native kidneys has also been recognized increasingly as a cause of kidney failure. We report the first case of PVAN occurring in the native kidneys of a solid-organ transplant recipient in Croatia as the eighth case described in the literature worldwide. A 65-year-old female with dilatative cardiomyopathy and good kidney function had a heart transplanted in 2012. Initial immunosuppressive therapy consisted of antithymocyte immunoglobulin with cyclosporine, mycophenolate mofetil and corticosteroids. Soon after transplantation, her kidney function began to fail progressively. Biopsy of the native kidneys revealed PVAN, and everolimus was introduced in immunosuppressive therapy. Nevertheless, her renal dysfunction progressed and she is now being evaluated for cadaveric kidney transplantation. PVAN should be considered in the differential diagnosis of new-onset renal failure following non-kidney solid organ transplantation. Early diagnosis is essential for prevention of irreversible renal damage.

Key words: polyomavirus-associated nephropathy, heart transplantation, kidney failure

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INTRODUCTION

Polyomavirus-associated nephropathy (PVAN) is a well-recognized cause of renal allograft dysfunction and allograft loss in renal transplant recipients, but it is an infrequent cause of nephropathy outside this setting. However, as outcomes following heart transplantation have improved significantly over the last years, chronic kidney disease (CKD) has become an increasingly prevalent complication in this population[(1)] and the number of PVAN of native kidneys reported in the literature is growing. We report the first case of PVAN occurring in the native kidneys of a solid-organ transplant recipient in Croatia as the eighth case described in the literature worldwide.

CASE REPORT

A female Caucasian patient born in 1940 was diagnosed with dilatative cardiomyopathy of unknown origin in 2011. Over a 2-year interval, she developed progressive congestive heart failure and due to deteriorating condition she underwent orthotopic cardiac transplantation on December 14, 2012. She had no concomitant illnesses and a good kidney function at the time of transplantation, with creatinine clearance 75-80 mL/min and proteinuria 0.31g/day. Unfortunately, data on kidney imaging studies done before transplantation were lost during the years. We can only presume that it was satisfactory.

The transplantation and immediate postoperative course were uneventful. Induction therapy included antithymocyte immunoglobulin with cyclosporine, mycophenolate mofetil (MMF) and corticosteroids. Serum creatinine immediately after transplantation was stable around 87-95 μmol/L. Four months after transplantation, the patient's kidney function began to deteriorate progressively without new-onset proteinuria or erythrocyturia. Cardiologist presumed that worsening of kidney function was due to calcineurin nephrotoxicity and in an attempt to reduce it 10 months after transplantation, the patient was switched from cyclosporine to tacrolimus. However, renal function continued to deteriorate further. Two years after transplantation, a nephrologist was consulted for the first time. Imaging studies revealed shrunken, chronically damaged kidneys with creatinine clearance of 35 mL/min and proteinuria 0.15 g/day. Also, BK viremia with 68,500 copies/mL was discovered. Biopsy of the native kidneys showed renal tubular cells with intranuclear inclusions characteristic of PVAN. Immunohistochemical staining for SV40 large T showed strong nuclear positivity in many distal tubular and collecting duct epithelial cells, which confirmed the diagnosis.

The patient had a stable heart function until that time, without any signs of rejection on repeated surveillance heart biopsies. Considering that, we decided to reduce immunosuppressive therapy by switching from tacrolimus to everolimus. Unfortunately, in a few days, the combination of everolimus with MMF and corticosteroids resulted in severe leukopenia that did not recover after reduction of MMF dose. Immunosuppression was changed again to tacrolimus with everolimus and corticosteroids while aiming at low levels (around 4 μg/L both).

After six months, the BK virus blood level fell to 1125 copies/mL, but renal dysfunction progressed further. Her creatinine clearance is now 13-10 mL/min and, as her heart function and overall clinical status is good, she is under evaluation for cadaveric kidney transplantation.

DISCUSSION

Chronic kidney disease and end-stage heart failure (HF) share multiple traditional risk factors such as hypertension, diabetes mellitus, and chronic glomerular ischemia due to poor renal perfusion. No wonder that up to one-third of all patients with New York Heart Association stage 3 or 4 end-stage HF have also evidence of CKD[2]. However, data on the evaluation of kidney function prior to orthotopic heart transplant are less well defined than liver transplant candidates and no formal guidelines exist. The objective of pretransplant evaluation is to establish the likelihood of being left with adequate kidney function after transplantation and the chance of progression to end-stage renal disease (Tablica 1).

Table 1

Proposition for kidney function assessment prior to orthotopic heart transplantation

Evaluation of kidney function prior to orthotopic heart transplantation
Complete patient history
Physical examination
Creatinine clearance
Total urinary protein excretion
Urinalysis
Urine culture
Kidney ultrasound (and color Doppler of renal arteries if necessary)
Kidney biopsy (if necessary)

Yet, kidney function is difficult to assess in patients with HF because they are frequently malnourished with low muscle mass and have edema. A normal or near normal serum creatinine level in this population does not necessarily reflect normal kidney function.

The degree of renal functional impairment posttransplant and the rate of CKD progression greatly depend on the extent of pretransplant kidney functional impairment, but also on the intra- and early postoperative course, the immunosuppressive regimen and individual clinical features that determine susceptibility to renal injury (patient age, presence of pretransplant diabetes and hypertension). The majority of cardiac transplant recipients will develop CKD within the first year after transplantation. They usually suffer an initial, rapid decline in renal function in the first two years posttransplant, which is followed by a less pronounced decline afterwards[3]. The mechanism underlying this biphasic pattern seems to be different kidney response to early versus late injuries.

Early after transplantation, kidney is exposed to perioperative and postoperative insults (surgical issues and complications, infections, etc.) and effect of calcineurin inhibitor therapy. After that, renal function stabilizes.

It seems that kidney function at the end of the first year posttransplant reflects renal function reserve and also predicts long-term renal outcome and mortality[4].

Late posttransplant kidney injury is a result of ongoing renal insults that accumulate from the traditional CKD risk factors (hypertension, new-onset diabetes after transplantation, and dyslipidemia)[5], and nephrotoxic effects of immunosuppressive drugs such as calcineurin inhibitors (CNI) (cyclosporine and tacrolimus) and mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus)[6]. Chronic CNI injury, clinically manifested by increased serum creatinine, sub-nephrotic range proteinuria, and bland urine sediment, is present in the majority of long-surviving, nonrenal transplant recipients. Kidney biopsy studies demonstrate histologic changes consistent with long-term CNI nephrotoxicity in 60%-70% of heart and liver transplant recipients with posttransplant end-stage renal disease[7]. Apart from direct nephrotoxic and hemodynamic effects that CNI cause through inhibition of nitric oxide and alterations in the RAAS[8], CNI, as also m-TOR inhibitors, cause metabolic changes (diabetes, hyperlipidemia, and hypertension) that contribute to development of kidney injury[9,10]. mTOR-inhibitors also promote development of anemia, potentiate CNI nephrotoxicity, and in some patients cause development of new-onset proteinuria[11].

There are several approaches to reducing CNI nephrotoxicity. The dose of CNI can be reduced with the addition of MMF, resulting in long-term renal functional improvement[12]. If the patient is taking cyclosporine, it can be switched to tacrolimus, as described in our case report. There are single-center case series, registry analyses, and multicenter studies demonstrating the benefit of tacrolimus over cyclosporine in both conversion and *de novo* heart settings[13]. Third strategy involves utilization of regimens that completely eliminate CNI with the introduction of m-TOR inhibitors. In some nonrenal organ recipients, while the elimination or minimization of calcineurin inhibitors has been associated with mild improvement in kidney function, this has often come at the expense of compromised immunosuppressive efficacy and worse patient outcomes[14].

Nephrotoxicity of CNI appears to be the major histologic feature in heart transplant recipients, but such injury may be indistinguishable from other unrelated kidney injuries such as chronic ischemia changes associated with atherosclerotic vascular disease[15] or PVAN[16,17]. PVAN is caused primarily by BK virus (BKV), but JC virus (JCV) and possibly simian virus SV40 may account for some cases. BKV is widely spread among people; however, it is clinically significant only in immunocompromised patients. Primary infection occurs most frequently in childhood and is usually innocent, but the virus stays latent in lymphoid cells and kidney epithelial cells (transitional, tubular and parietal cells of Bowman capsule). The most important risk factor for development of PVAN is the level of immunosuppression and some consider development of BKV replication a clear sign of too high level of immunosuppression. Various combinations of immunosuppressive drugs have been linked with development of PVAN; however, we still lack clear evidence for this connection. PVAN has been proven in patients receiving almost every possible immunosuppressive drugs or their combination. Besides immunosuppressive drugs, risk factors for development of PVAN are older or younger age, male gender, CMV infection, acute rejection treatment, white race and use of corticosteroids.

Polyomavirus-associated nephropathy appears to be a rare cause of renal failure in heart transplant recipients with only eight cases published in the literature, but is it really so? Renal biopsy is the gold standard for diagnosing PVAN[18] and also the only method to distinguish it from CNI nephrotoxicity. However, the high incidence of CNI nephrotoxicity in heart transplant recipients has led to a common assumption that every renal failure in this population can be attributed to CNI toxicity, without renal histopathologic evaluation. This assumption leads to changes in immunosuppression that can further worsen PVAN and cause unnecessary delay in establishing the true cause of renal failure. PVAN should be considered in the differential diagnosis when evaluating worsening kidney function after heart transplantation and a more proactive approach in search for the cause of kidney failure could result in a higher prevalence of PVAN in this patient population.

Treatment of PVAN remains a problem. It is based on the adjustment of immunosuppressive regimens and the empiric use of adjuvant antiviral therapy. Unfortunately, treatment is very often ineffective and preventive screening for BKV replication and empiric reduction of immunosuppression is still the preferred approach[19]. However, BKV replication surveillance studies of non-kidney solid-organ recipients are lacking and the value of regular monitoring of BKV replication in non-kidney transplant recipients is still not clear.

CONCLUSION

Kidney injury in heart transplant recipients is a common problem with serious consequences. Active approach should be taken in establishing the cause of kidney failure and PVAN should be considered in differential diagnosis. We need more studies to determine the value of regular monitoring for BKV replication in heart transplant recipients.

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SAŽETAK

NEFROPATIJA UZROKOVANA BK VIRUSOM U BOLESNIKA S TRANSPLANTIRANIM SRCEM: PRVI DOKUMENTIRANI SLUČAJ U HRVATSKOJ

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Unazad nekoliko godina sa značajnim poboljšanjem preživljenja bolesnika s transplantiranim srcem kronično zatajenje bubrega postalo je sve češća komplikacija u toj populaciji. Nefropatija uzrokovana poliomavirusom (PVAN) nativnih bubrega također se sve češće prepoznaje kao uzrok zatajenja bubrega. Prikazujemo prvi slučaj PVAN nativnih bubrega kod primatelja transplantata solidnog organa u Hrvatskoj i osmi takav slučaj dosad opisan u literaturi. Bolesnici u dobi od 65 godina s dilatativnom kardiomiopatijom i dobrom bubrežnom funkcijom je 2012. godine transplantirano srce. Inicijalna imunosupresivna terapija sastojala se od antitimocitnog imunoglobulina s ciklosporinom, mikofenolat mofetilom i kortikosteroidima. Ubrzo nakon transplantacije dolazi do zatajenja bubrega. Biopsijom nativnih bubrega postavljena je dijagnoza PVAN, a u imunosupresivnu terapiju je uveden everolimus. Usprkos tome dolazi do daljnjeg napredovanja zatajenja bubrega i bolesnica je trenutno u pripremi za kadaveričnu transplantaciju bubrega. PVAN treba razmotriti u diferencijalnoj dijagnozi novonastalog zatajenja bubrega nakon transplantacije solidnih organa. Rana dijagnoza PVAN je bitna u sprječavanju razvoja ireverzibilnog bubrežnog zatajenja.

Ključne riječi: poliomavirusna nefropatija, transplantacija srca, zatajivanje bubrega